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(57) Abstract

This invention provides a method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus by administering to a patient a therapeutically effective amount of a thiazolidione derivative and/or a related compound.

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A METHOD OF REDUCING THE AMOUNT OF EXOGENOUS INSULIN ADMINISTERED TO A PATIENT HAVING NONINSULIN-DEPENDENT DIABETES MELLITUS

FIELD OF THE INVENTION

The present invention provides a method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus.

BACKGROUND OF THE INVENTION

Diabetes is one of the most prevalent chronic disorders worldwide with significant personal and financial costs for patients and their families, as well as for society. Different types of diabetes exist with distinct etiologies and pathogeneses. For example, diabetes mellitus is a disorder of carbohydrate metabolism, characterized by hyperglycemia and glycosuria and resulting from inadequate production or utilization of insulin.

Noninsulin-dependent diabetes mellitus (NIDDM), or Type II diabetes, is a form of diabetes mellitus that occurs predominantly in adults in whom adequate production of insulin is available for use, yet a defect exists in insulin-mediated utilization and metabolism of glucose in peripheral tissues.

Overt NIDDM is characterized by three major metabolic abnormalities: resistance to insulin-mediated glucose disposal; impairment of nutrient-stimulated insulin secretion; and overproduction of glucose by the liver.

Failure to treat NIDDM (i.e., control blood glucose levels) can result in mortality due to cardiovascular disease and in other diabetic complications including retinopathy, nephropathy, and peripheral neuropathy.

The treatment of NIDDM to control blood glucose levels in patients having NIDDM has included diet and exercise, as well as the use of sulfonylurea and biguanide therapeutic compounds. In addition, the compounds metformin and acarbose have recently been used to treat patients having NIDDM. However, in some patients, hyperglycemia cannot be adequately controlled by diet and exercise and/or the use of such therapeutic compounds. In such cases, exogenous insulin must be administered to the patient. The administration of insulin by injection to a patient, in addition to being expensive and painful, can result in various conditions or complications that are detrimental to the patient. For example, an insulin reaction (hypoglycemia) can occur because of an error in insulin dosage, a missed meal, unplanned exercise or without apparent cause. In addition, local and/or generalized allergic reactions and immunological resistance to insulin can occur.

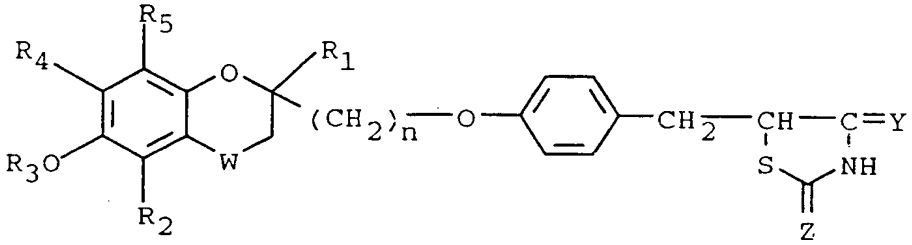
Thus, the present invention is a method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus. A partial or total reduction of the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus can also be called "insulin rescue" as the patient is rescued from the need to use exogenous insulin to control serum glucose levels. As described below, in ongoing clinical trials 7 out of 17 human patients given a compound of the present method were completely removed or rescued from the need for exogenous insulin, a very exciting and unexpected discovery, as it was thought by

those skilled in the art that a patient having NIDDM and requiring insulin suffered from insulin resistance and B-cell failure. B-cells are the cells in the pancreas that make endogenous insulin.

See, for example, Saad M.F., in The American Journal of Medicine, 1991;90:229-235, which discusses the role of pancreatic B-cell burnout in the progression of insulin resistance to NIDDM.

SUMMARY OF THE INVENTION

The present invention provides a method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus comprising administering to a patient a therapeutically effective amount of a compound of Formula I



I

wherein R_1 and R_2 are the same or different and each represents a hydrogen atom or a C_1-C_5 alkyl group;

R_3 represents a hydrogen atom, a C_1-C_6 aliphatic acyl group, an alicyclic acyl group, an aromatic acyl group, a heterocyclic acyl group, an araliphatic acyl group, a (C_1-C_6 alkoxy)carbonyl group, or an aralkyloxycarbonyl group;

R_4 and R_5 are the same or different and each represents a hydrogen atom, a C_1-C_5 alkyl group or a C_1-C_5 alkoxy group, or R_4 and R_5 together represent a C_1-C_4 alkylenedioxy group;

n is 1, 2, or 3;

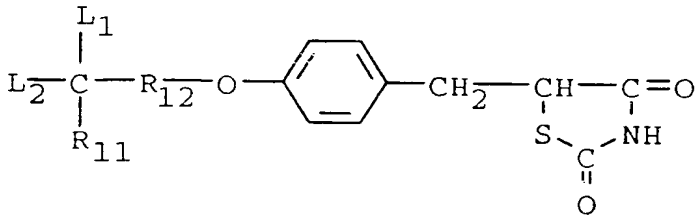
W represents the $-CH_2-$, CO, or $CH-OR_6$ group (in which R_6 represents any 1 of the atoms or groups defined for R_3 and may be the same as or different from R_3); and

Y and Z are the same or different and each represents an oxygen atom or an imino (=NH) group;

and pharmaceutically acceptable salts thereof.

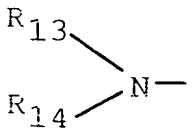
In a preferred embodiment of the method, the compound of Formula I is 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]-phenyl]methyl]-2,4-thiazolidinedione.

Another embodiment provides a method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus, the method comprising administering to a patient having noninsulin-dependent diabetes mellitus a therapeutically effective amount of a compound of Formula II



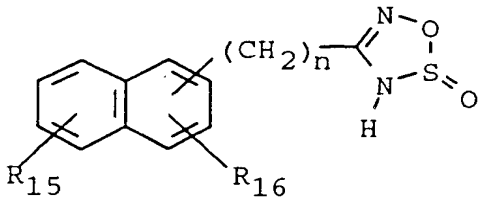
II

wherein R_{11} is substituted or unsubstituted alkyl, alkoxy, cycloalkyl, phenylalkyl, phenyl, aromatic acyl group, a 5- or 6-membered heterocyclic group including 1 or 2 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, or a group of the formula



wherein R_{13} and R_{14} are the same or different and each is lower alkyl or R_{13} and R_{14} are combined to each other either directly or as interrupted by a heteroatom selected from the group consisting of nitrogen, oxygen, and sulfur to form a 5- or 6-membered ring; wherein R_{12} means a bond or a lower alkylene group; and wherein L_1 and L_2 are the same or different and each is hydrogen or lower alkyl or L_1 and L_2 are combined to form an alkylene group, or a pharmaceutically acceptable salt thereof.

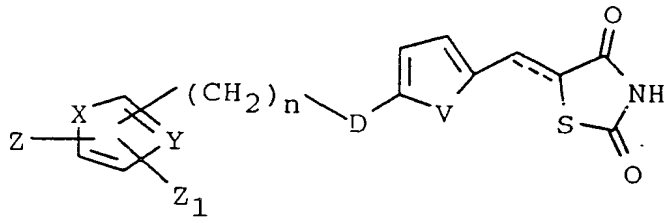
Also provided is a method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus, the method comprising administering to a patient having noninsulin-dependent diabetes mellitus a therapeutically effective amount of a compound of Formula III



III

wherein R_{15} and R_{16} are independently hydrogen, lower alkyl containing 1 to 6 carbon atoms, alkoxy containing 1 to 6 carbon atoms, halogen, ethynyl, nitrile, methylthio, trifluoromethyl, vinyl, nitro, or halogen substituted benzyloxy; n is 0 to 4 and the pharmaceutically acceptable salts thereof.

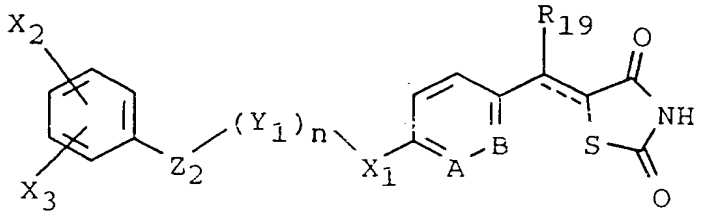
The present invention also provides a method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus, the method comprising administering to a patient having noninsulin-dependent diabetes mellitus a therapeutically effective amount of a compound of Formula IV



IV

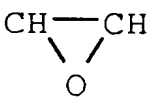
wherein the dotted line represents a bond or no bond;
V is -CH = CH-, -N = CH-, -CH = N- or S;
D is CH_2, CHOH, CO, C = NOR_{17} or CH = CH;
X is S, O, NR_{18}, -CH = N or -N = CH;
Y is CH or N;
Z is hydrogen, (C_1-C_7) alkyl, (C_3-C_7)cycloalkyl, phenyl, naphthyl, pyridyl, furyl, thienyl, or phenyl mono- or disubstituted with the same or different groups which are (C_1-C_3)alkyl, trifluoromethyl, (C_1-C_3)alkoxy, fluoro, chloro, or bromo;
Z_1 is hydrogen or (C_1-C_3)alkyl;
R_{17} and R_{18} are each independently hydrogen or methyl; and n is 1, 2, or 3; the pharmaceutically acceptable cationic salts thereof; and the pharmaceutically acceptable acid addition salts thereof when the compound contains a basic nitrogen.

In another embodiment, the present invention provides a method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus, the method comprising administering to a patient having noninsulin-dependent diabetes mellitus a therapeutically effective amount of a compound of Formula V

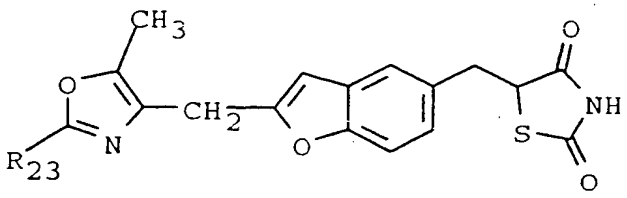


V

wherein the dotted line represents a bond or no bond;
A and B are each independently CH or N, with the proviso that when A or B is N, the other is CH;

X_1 is S, SO, SO_2, CH_2, CHOH, or CO;
n is 0 or 1;
Y_1 is CHR_{20} or R_{21}, with the proviso that when n is 1 and Y_1 is NR_{21}, X_1 is SO_2 or CO;
Z_2 is CHR_{22}, CH_2CH_2, CH=CH,  , OCH_2, SCH_2, $SOCH_2$, or SO_2CH_2;
R_{19}, R_{20}, R_{21}, and R_{22} are each independently hydrogen or methyl; and
X_2 and X_3 are each independently hydrogen, methyl, trifluoromethyl, phenyl, benzyl, hydroxy, methoxy, phenoxy, benzyloxy, bromo, chloro, or fluoro;
a pharmaceutically acceptable cationic salt thereof; or a pharmaceutically acceptable acid addition salt thereof when A or B is N.

In another embodiment, the present invention provides a method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus, the method comprising administering to a patient having noninsulin-dependent diabetes mellitus a therapeutically effective amount of a compound of Formula VI

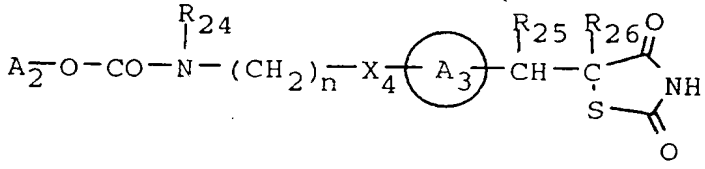


VI

or a pharmaceutically acceptable salt thereof, wherein R_{23} is alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, phenyl, or mono- or disubstituted phenyl wherein said substituents are independently alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 3 carbon atoms, halogen, or trifluoromethyl.

In another embodiment, the present invention provides a method of reducing the amount of exogenous insulin administered to a patient having noninsulin-

dependent diabetes mellitus, the method comprising administering a therapeutically effective amount of a compound of Formula VII



VII

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A_2 represents an alkyl group, a substituted or unsubstituted aryl group, or an aralkyl group wherein the alkylene or the aryl moiety may be substituted or unsubstituted;

A_3 represents a benzene ring having in total up to 3 optional substituents;

R_{24} represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group wherein the alkyl, or the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group; or

A_2 together with R_{24} represents substituted or unsubstituted C_{2-3} polymethylene group, optional substituents for the polymethylene group being selected from alkyl or aryl or adjacent substituents together with the methylene carbon atoms to which they are attached form a substituted or unsubstituted phenylene group;

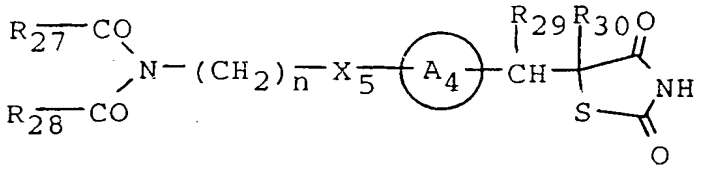
R_{25} and R_{26} each represent hydrogen, or R_{25} and R_{26} together represent a bond;

X_4 represents O or S; and

n represents an integer in the range of from 2 to 6.

In another embodiment, the present invention provides a method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus, the method comprising

administering to a patient having noninsulin-dependent diabetes mellitus a therapeutically effective amount of a compound of Formula VIII



VIII

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate therefor, wherein:

R_{27} and R_{28} each independently represent an alkyl group, a substituted or unsubstituted aryl group, or an aralkyl group being substituted or unsubstituted in the aryl or alkyl moiety; or

R_{27} together with R_{28} represents a linking group, the linking group consisting of an optionally substituted methylene group and either a further optionally substituted methylene group or an O or S atom, optional substituents for the said methylene groups being selected from alkyl-, aryl, or aralkyl, or substituents of adjacent methylene groups together with the carbon atoms to which they are attached form a substituted or unsubstituted phenylene group;

R_{29} and R_{30} each represent hydrogen, or R_{29} and R_{30} together represent a bond;

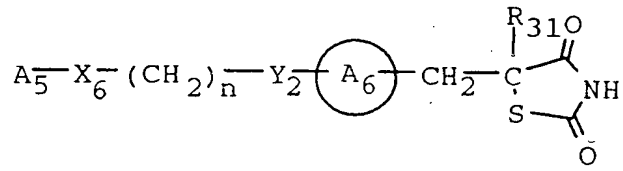
A_4 represents a benzene ring having in total up to 3 optional substituents;

X_5 represents O or S; and

n represents an integer in the range of from 2 to 6.

In another embodiment, the present invention provides a method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus, the method comprising administering to a patient having noninsulin-dependent

diabetes mellitus a therapeutically effective amount of a compound of Formula IX



IX

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A_5 represents a substituted or unsubstituted aromatic heterocyclyl group;

A_6 represents a benzene ring having in total up to 5 substituents;

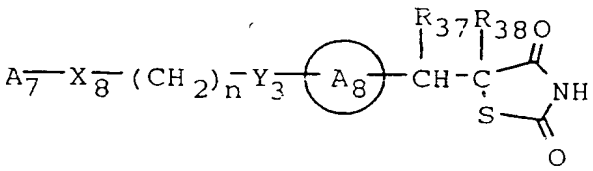
X_6 represents O, S, or NR_{32} wherein R_{32} represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

Y_2 represents O or S;

R_{31} represents an alkyl, aralkyl, or aryl group; and

n represents an integer in the range of from 2 to 6.

In another embodiment, the present invention provides a method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus, the method comprising administering to a patient having noninsulin-dependent diabetes mellitus a therapeutically effective amount of a compound of Formula X



X

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A_7 represents a substituted or unsubstituted aryl group;

A_8 represents a benzene ring having in total up to 5 substituents;

X_8 represents O, S, or NR_{39} wherein R_{39} represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

Y_3 represents O or S;

R_{37} represents hydrogen;

R_{38} represents hydrogen or an alkyl, aralkyl, or aryl group or R_{37} together with R_{38} represents a bond; and

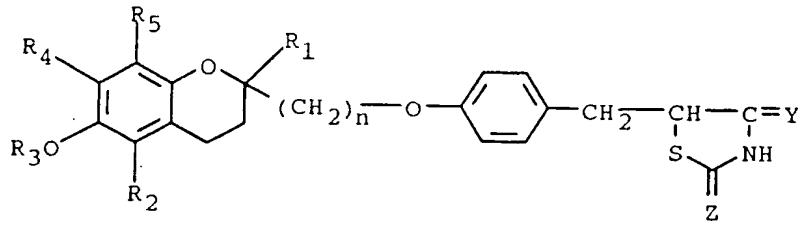
n represents an integer in the range of from 2 to 6.

BRIEF DESCRIPTION OF THE DRAWING

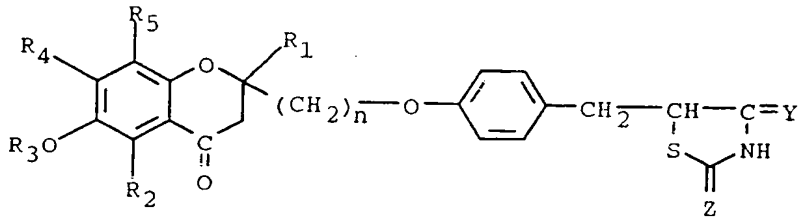
Figure 1 shows a chart representing patients' mean blood glucose levels and mean total daily exogenous insulin over time with the administration of a compound of the present method.

DETAILED DESCRIPTION OF THE INVENTION

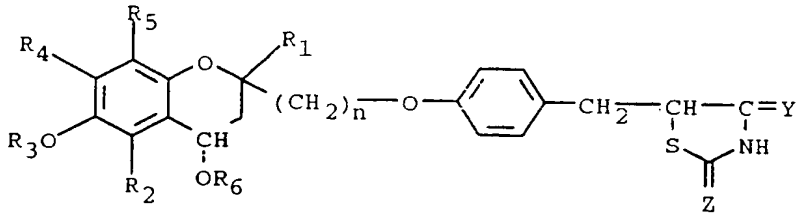
Compounds used in the method of the present invention, which are 5-[4-(chromoanalkoxy)benzyl] thiazolidene derivatives, may be represented by the Formulas (Ia), (Ib), and (Ic)



(Ia)



(Ib)



(Ic)

(in which R_1, R_2, R_3, R_4, R_5, R_6, n, Y, and Z are as defined above) and include pharmaceutically acceptable salts thereof.

In the compounds of the invention, where R_1 or R_2 represents an alkyl group, the alkyl group may be a straight or branched chain alkyl group having from 1 to 5 carbon atoms and is preferably a primary or secondary alkyl group, for example the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, or isopentyl group.

Where R_3 or R_6 represents an aliphatic acyl group, the aliphatic acyl group preferably has from 1 to 6 carbon atoms and can include one or more carbon-carbon double or triple bonds. Examples of such groups include the formyl, acetyl, propionyl, butyryl, isobutyryl, pivaloyl, hexanoyl, acryloyl, methacryloyl, and crotonyl groups.

Where R_3 or R_6 represents an alicyclic acyl group, it is preferably a cyclopentanecarbonyl, cyclohexanecarbonyl, or cycloheptanecarbonyl group.

Where R_3 or R_6 represents an aromatic acyl group, the aromatic moiety thereof may optionally have one or more substituents (for example, nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl, or hydroxy substituents); examples of such aromatic acyl groups included the benzoyl, p-nitrobenzoyl, m-fluorobenzoyl, o-chlorobenzoyl, p-aminobenzoyl, m-(dimethylamino)benzoyl, o-methoxybenzoyl, 3,4-dichlorobenzoyl, 3,5-di-t-butyl-4-hydroxybenzoyl, and 1-naphthoyl groups.

Where R_3 or R_6 represents a heterocyclic acyl group, the heterocyclic moiety thereof preferably has one or more, preferably one, oxygen, sulfur, or nitrogen heteroatoms and has from 4 to 7 ring atoms; examples of such heterocyclic acyl groups include the 2-furoyl, 3-thenoyl, 3-pyridinecarbonyl (nicotinoyl), and 4-pyridinecarbonyl groups.

Where R_3 or R_6 represents an araliphatic acyl group, the aliphatic moiety thereof may optionally have one or more carbon-carbon double or triple bonds and the aryl moiety thereof may optionally have one or more substituents (for example, nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl, or hydroxy substituents); examples of such araliphatic acyl groups include the phenylacetyl, p-chlorophenylacetyl, phenylpropionyl, and cinnamoyl groups.

Where R_3 or R_6 represents a (C_1-C_6 alkoxy)carbonyl group, the alkyl moiety thereof may be any one of those alkyl groups as defined for R_1 and R_2, but is preferably a methyl or ethyl group, and the alkoxycarbonyl group represented by R_3 or R_6 is therefore preferably a methoxycarbonyl or ethoxycarbonyl group.

Where R_3 or R_6 represents an aralkyloxycarbonyl group, the aralkyl moiety thereof may be any one of those included within the araliphatic acyl group represented by R_3 or R_6, but is preferably a benzyloxycarbonyl group.

Where R_4 and R_5 represent alkyl groups, the alkyl groups can be the same or different and can be straight or branched chain alkyl groups. The alkyl groups preferably have from 1 to 5 carbon atoms and examples include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, and isopentyl groups.

Where R_4 and R_5 represent alkoxy groups, the alkoxy groups can be the same or different and can be straight or branched chain groups, preferably having from 1 to 4 carbon atoms. Examples include the methoxy, ethoxy, propoxy, isopropoxy, and butoxy groups. Alternatively, R_4 and R_5 can together represent a C_1-C_4 alkylenedioxy group, more preferably a methylenedioxy or ethylenedioxy group.

Preferred classes of compounds of Formula I are as follows:

(1) Compounds in which R_3 represents a hydrogen atom, a C_1-C_6 aliphatic acyl group, an aromatic acyl group, or a heterocyclic acyl group.

(2) Compounds in which Y represents an oxygen atom; R_1 and R_2 are the same or different and each represents a hydrogen atom or a C_1-C_5 alkyl group; R_3 represents a hydrogen atom, a C_1-C_6 aliphatic acyl group, an aromatic acyl group, or a pyridinecarbonyl group; and R_4 and R_5 are the same or different and each represents a hydrogen atom, a C_1-C_5 alkyl group, or a C_1 or C_2 alkoxy group.

(3) Compounds as defined in (2) above, in which: R_1, R_2, R_4, and R_5 are the same or different and each represents a hydrogen atom or a C_1-C_5 alkyl group; n is 1 or 2; and W represents the $-CH_2-$ or >CO group.

(4) Compounds as defined in (3) above, in which R_3 represents a hydrogen atom, a C_1-C_5 aliphatic acyl group, a benzoyl group, or a nicotinyl group.

(5) Compounds as defined in (4) above, in which: R_1 and R_4 are the same or different and each represents a C_1-C_5 alkyl group; R_2 and R_5 are the same or different and each represents the hydrogen atom or the methyl group; and R_3 represents a hydrogen atom or a C_1-C_4 aliphatic acyl group.

(6) Compounds in which: W represents the $-CH_2-$ or >CO group; Y and Z both represent oxygen atoms; n is 1 or 2; R_1 and R_4 are the same or different and each represents a C_1-C_4 alkyl group; R_2 and R_5 are the same or different and each represents the hydrogen atom or the methyl group; and R_3 represents a hydrogen atom or a C_1-C_4 aliphatic acyl group.

(7) Compounds as defined in (6) above, in which n is 1.

(8) Compounds as defined in (6) or (7) above, in which W represents the $-CH_2-$ group.

Preferred compounds among the compounds of Formula I are those wherein:

R_1 is a C_1-C_4 alkyl group, more preferably a methyl or isobutyl group, most preferably a methyl group;

R_2 is a hydrogen atom or a C_1-C_4 alkyl group, preferably a hydrogen atom, or a methyl or isopropyl group, more preferably a hydrogen atom or a methyl group, most preferably a methyl group;

R_3 is a hydrogen atom, a C_1-C_4 aliphatic acyl group, an aromatic acyl group or a pyridinecarbonyl group, preferably a hydrogen atom, or an acetyl, butyryl, benzoyl, or nicotinyl group, more preferably a hydrogen atom or an acetyl, butyryl or benzoyl group, most preferably a hydrogen atom or an acetyl group;

R_4 is a hydrogen atom, a C_1-C_4 alkyl group or a C_1 or C_2 alkoxy group, preferably a methyl, isopropyl, t-butyl, or methoxy group, more preferably a methyl or t-butyl group, most preferably a methyl group;

R_5 is a hydrogen atom, a C_1-C_4 alkyl group or a C_1 or C_2 alkoxy group, preferably a hydrogen atom, or a methyl or methoxy group, more preferably a hydrogen atom or a methyl group, and most preferably a methyl group;

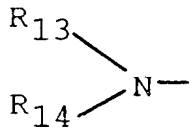
n is 1 or 2, preferably 1;

Y is an oxygen atom;

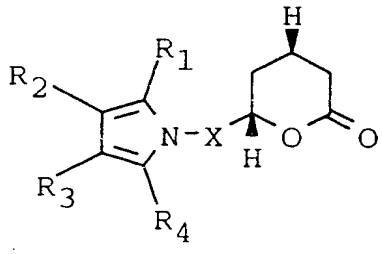
Z is an oxygen atom or an imino group, most preferably an oxygen atom; and

W is a $-CH_2-$ or $>C=O$ group, preferably a $-CH_2-$ group.

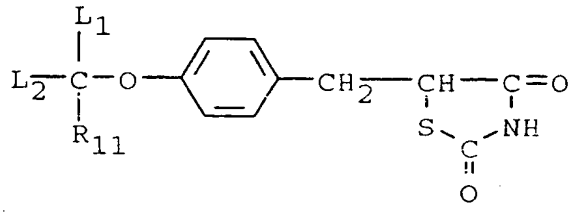
Referring to the general Formula II, the substituents may be any from 1 to 3 selected from nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl, or hydroxy, the aromatic acyl group may be benzoyl and naphthoyl. The alkyl group R_{11} may be a straight chain or branched alkyl of 1 to 10 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, and n-decyl; the cycloalkyl group R_{11} may be a cycloalkyl group of 3 to 7 carbon atoms, such as cyclopropyl, cyclopentyl, cyclohexyl, and cycloheptyl; and the phenylalkyl group R_{11} may be a phenylalkyl group of 7 to 11 carbon atoms such as benzyl and phenethyl. As examples of the heterocyclic group R_{11} may be mentioned 5- or 6-membered groups each including 1 or 2 hetero-atoms selected from among nitrogen, oxygen, and sulfur, such as pyridyl, thienyl, furyl, thiazolyl, etc. When R_{11} is



the lower alkyls R_{13} and R_{14} may each be a lower alkyl of 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, and n-butyl. When R_{13} and R_{14} are combined to each other to form a 5- or 6-membered heterocyclic group as taken together with the adjacent N atom, i.e., in the form of



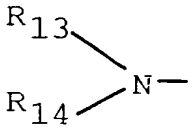
this heterocyclic group may further include a heteroatom selected from among nitrogen, oxygen, and sulfur as exemplified by piperidino, morpholino, pyrrolidino, and piperazino. The lower alkylene group R_{12} may contain 1 to 3 carbon atoms and thus may be, for example, methylene, ethylene, or trimethylene. The bond R_{12} is equivalent to the symbol "-", ".", or the like which is used in chemical structural formulas, and when R_{12} represents such a bond, the compound of general Formula II is represented by the following general Formula II(a)



II(a)

Thus, when R_{12} is a bond, the atoms adjacent thereto on both sides are directly combined together. As examples

of the lower alkyls L_1 and L_2, there may be mentioned lower alkyl groups of 1 to 3 carbon atoms, such as methyl and ethyl. The alkylene group formed as L_1 and L_2 are joined together is a group of the formula $-(CH_2)_n-$ [where n is an integer of 2 to 6]. The cycloalkyl, phenylalkyl, phenyl, and heterocyclic groups mentioned above, as well as said heterocyclic group



may have 1 to 3 substituents in optional positions on the respective rings. As examples of such substituents may be mentioned lower alkyls (e.g., methyl, ethyl, etc.), lower alkoxy groups (e.g., methoxy, ethoxy, etc.), halogens (e.g., chlorine, bromine, etc.), and hydroxyl. The case also falls within the scope of the general Formula II that an alkylenedioxy group of the formula $-O-(CH_2)_m-O-$ [is an integer of 1 to 3], such as methylenedioxy, is attached to the two adjacent carbon atoms on the ring to form an additional ring.

The preferred compounds of Formula III are those wherein R_{15} and R_{16} are independently hydrogen, lower alkyl containing 1 to 6 carbon atoms, alkoxy containing 1 to 6 carbon atoms, halogen, ethynyl, nitrile, trifluoromethyl, vinyl, or nitro; n is 1 or 2 and the pharmaceutically acceptable salts thereof.

Preferred in Formula IV are compounds wherein the dotted line represents no bond, particularly wherein D is CO or CHOH. More preferred are compounds wherein V is -CH = CH-, -CH = N-, or S and n is 2, particularly those compounds wherein X is O and Y is N, X is S and Y is N, X is S and Y is CH or X is -CH = N- and Y is CH. In the most preferred compounds X is O or S

and Y is N forming an oxazol-4-yl, oxazol-5-yl, thiazol-4-yl, or thiazol-5-yl group; most particularly a 2-[(2-thienyl), (2-furyl), phenyl, or substituted phenyl]-5-methyl-4-oxazolyl group.

The preferred compounds in Formula V are:

a) those wherein the dotted line represents no bond, A and B are each CH, X_1 is CO, n is 0, R_{19} is hydrogen, Z_2 is CH_2CH_2 or CH=CH and X_3 is hydrogen, particularly when X_2 is hydrogen, 2-methoxy, 4-benzyloxy, or 4-phenyl;

b) those wherein A and B are each CH, X_1 is S or SO_2, n is 0, R_{19} is hydrogen, Z_2 is CH_2CH_2, and X_3 is hydrogen, particularly when X_2 is hydrogen or 4-chloro.

A preferred group of compounds is that of Formula VI wherein R_{23} is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, phenyl, halophenyl, or $(C_1\text{-}C_6)$alkylphenyl. Especially preferred within this group are the compounds where R_{23} is phenyl, methylphenyl, fluorophenyl, chlorophenyl, or cyclohexyl.

When used herein with regard to Formulas VII through X, the term "aryl" includes phenyl and naphthyl, substituted phenyl, optionally substituted with up to 5, preferably up to 3, groups selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxy, amino, nitro, carboxy, alkoxycarbonyl, alkoxycarbonyl alkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

The term "halogen" refers to fluorine, chlorine, bromine, and iodine; preferably chlorine.

The terms "alkyl" and "alkoxy" relate to groups having straight or branched carbon chains, containing up to 12 carbon atoms.

Suitable alkyl groups are $C_{1\text{-}12}$ alkyl groups, especially $C_{1\text{-}6}$ alkyl groups, e.g., methyl, ethyl,

n-propyl, iso-propyl, n-butyl, isobutyl, or tert-butyl groups.

Suitable substituents for any alkyl group include those indicated above in relation to the term "aryl".

Suitable substituents for any heterocyclyl group include up to 4 substituents selected from the group consisting of alkyl, alkoxy, aryl, and halogen or any 2 substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, preferably a benzene ring, and wherein the carbon atoms of the aryl group represented by the said 2 substituents may themselves be substituted or unsubstituted.

A most preferred compound of the present invention is:

5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione.

Other preferred compounds of the present method include ciglitazone, pioglitazone, darglitazone, englitazone, and BRL 49653.

Ciglitazone is also known as 5-[p-[(1-Methylcyclohexyl)methoxy]benzyl]-2,4-thiazolidinedione.

Pioglitazone is also known as 5-[p-[2-(5-Ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione.

Darglitazone is also known as 5-[p-[3-(5-Methyl-2-phenyl-4-oxazolyl)propionyl]benzyl]-2,4-thiazolidinedione.

Englitazone is also known as 5-[[(2R)-2-Benzyl-6-chromanyl]methyl]-2,4-thiazolidinedione.

BRL 49653 is also known as 5-[(4-[2-Methyl-2-(prindinylamino)ethoxy]phenyl)methyl]-2,4-thiazolidinedione-(Z)-2-butenedioate (1:1).

The term "patient" includes humans and other animals. The term "exogenous insulin" means insulin which is administered to a patient from an external

source as compared to endogenous insulin, which is insulin that is secreted by the pancreas of the patient.

The phrase "reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus" means that in a patient requiring the control of blood sugar levels using exogenous insulin, the amount of insulin required to achieve the desired control of blood sugar levels in the absence of a compound of the present invention is more than the amount of insulin required when a compound of the present invention is administered to the patient. It is also intended that the term "reduction" include complete cessation of the administration of exogenous insulin to a patient.

It is surprising and unexpected that patients requiring exogenous insulin because their blood glucose levels could not be adequately controlled by diet and exercise and/or any of the commonly used therapeutic substances could be completely removed from insulin and that adequate control of blood glucose could be achieved by the administration of a compound of the present method. Thus, the present method provides a way of treating the most severe cases of noninsulin-dependent diabetes mellitus-those requiring exogenous insulin. Moreover, the present method provides for the complete cessation of exogenous insulin administration in those patients where insulin had heretobefore been required.

In general, it is desired to control the fasting blood glucose levels of patients having NIDDM in the range of about 80 mg/dL to about 140 mg/dL, which is the normal range as defined by the American Diabetes Association. The range of about 150 mg/dL to about 200 mg/dL has been considered as providing adequate control. Generally, a person having diabetes mellitus

has been defined as a person having a fasting glucose of 140 mg/dL or higher.

The patients of the present method typically show a C-peptide level (fasting) that is 1.5 ng/mL or higher.

The compounds of Formulas I through X are capable of further forming both pharmaceutically acceptable acid addition and/or base salts. All of these forms are within the scope of the present invention.

Pharmaceutically acceptable acid addition salts of the compounds of Formulas I through X include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate, n-methyl glucamine (see, for example, Berge S.M., et al., "Pharmaceutical Salts," Journal of Pharmaceutical Science, 1977;66:1-19).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a

sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner or as above. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge S.M., et al., "Pharmaceutical Salts," Journal of Pharmaceutical Science, 1977;66:1-19).

The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner or as above. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the

solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in different configurations. The compounds can, therefore, form stereoisomers. Although these are all represented herein by a limited number of molecular formulas, the present invention includes the use of both the individual, isolated isomers and mixtures, including racemates, thereof. Where stereospecific synthesis techniques are employed or optically active compounds are employed as starting materials in the preparation of the compounds, individual isomers may be prepared directly; on the other hand, if a mixture of isomers is prepared, the individual isomers may be obtained by conventional resolution techniques, or the mixture may be used as it is, without resolution.

Furthermore, the thiazolidene part of the compound of Formulas I through X can exist in the form of tautomeric isomers. All of the tautomers are represented by Formulas I through X, and are intended to be a part of the present invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsules, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 600 mg preferably 0.5 mg to 400 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a

particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

The compounds of the present invention, and methods of making these compounds, are known and disclosed in U.S. Patents 5,223,522 issued June 29, 1993; 5,132,317 issued July 12, 1992; 5,120,754 issued June 9, 1992; 5,061,717 issued October 29, 1991; 4,897,405 issued January 30, 1990; 4,873,255 issued October 10, 1989; 4,687,777 issued August 18, 1987; 4,572,912, issued February 25, 1986; and 4,287,200, issued September 1, 1981. These issued patents are incorporated herein by reference.

The examples presented below are intended to illustrate particular embodiments of the invention, and are not intended to limit the specification, including the claims, in any manner.

EXAMPLE

Clinical Study - Study of 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione in NIDDM Patients Requiring Insulin

Study Protocol

After meeting the patient selection criteria set forth below, all patients participating in the study took 400 mg of 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione per day (in the form of two 200 mg tablets) while initially maintaining

their current insulin therapy. Every two weeks, fasting serum glucose (FSG) hemoglobin A_{1c} (HbA_{1c}), C-peptide, and total insulin measurements were made. Home diaries were used to monitor blood glucose levels between visits to the clinic and to make clinical judgments for insulin dosage adjustments at clinic visits. Based on home diary information of the prior two weeks, the insulin dose was adjusted accordingly. At the first visit that glycemic control was achieved, the insulin dose was decreased to half the value at baseline. At subsequent visits to the clinic, if glycemic control was still evident, the current insulin dose was halved. This reduction continued until the patient no longer required exogenous insulin.

Patient Selection

Patients were to: 1) have NIDDM as defined by the criteria of the National Diabetes Data Group; 2) have evidence of failure of blood sugar control on sulfonylureas; 3) have evidence of poor control as documented by a glycosylated hemoglobin above the normal range (i.e., HbA_{1c} greater than the upper limit of normal); 4) have a C-peptide greater than 1.5 ng/mL; 5) be over 18 years of age; and 6) have concomitant therapy with insulin for 6 months or less.

The study enrolled 17 patients over a 2-week period at a single center. All patients had a 2-week baseline period in which they maintained their dose of insulin at a constant level and performed home glucose monitoring 2-3 times/day. This frequency of home glucose monitoring was maintained during the study and values were recorded on diary cards. These were examined during the course of the study at 2-week intervals. The investigators was instructed to decrease a patient's dose of insulin at these visits if

the glycemic control appeared to be improved or stable based on the glucose monitoring levels or at any time during the study if a reduction were required for safety reasons. Similarly, the investigator could increase insulin doses if glycemic control appeared to worsen. The data represents 8 weeks of data from a 12-week study, the last 4 weeks of which are still in progress.

Patient Characteristics

17 Patients	(10 males, 7 females)
Mean Age (Range):	57 years (35-72)
Mean Weight	104 kg (76-126)
Mean HbA1c:	11.8% (8.6-15.4)
Mean C-peptide	2.8 ng/mL (1.5-4.2)
Mean Blood Glucose	205 mg/dL (101-363)
Mean Duration Diabetes	11 years (2-31)
Mean Duration Insulin Use	4 years (6 months-15 years)
Mean Insulin Dose	58 units/day (20-21)

Results

As stated above, this summary represents 8-week interim data from a 12-week study. Based upon a favorable decrease in blood glucose levels, all 17 patients have had their dose of insulin reduced or discontinued. The mean decrease in insulin dose is 60% with a range of 30% to 100%. The glucose levels have decreased by 10% (20 mg/dL) in the total group with a range of 0 to 133 mg/dL). (See Figure 1.)

A total of 7 patients have had their insulin discontinued at this time (8 weeks). These patients have not had an overall decrease in their mean blood

glucose as a group but have maintained their mean level of 160 mg/dL with a decrease from 42 units/day of insulin to 0. Three of these patients have decreased their fasting blood glucose to a level below 140 mg/dL. Four of the 7 patients have been off insulin for over a month with maintenance of their glucose control. All seven are currently being maintained on 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione.

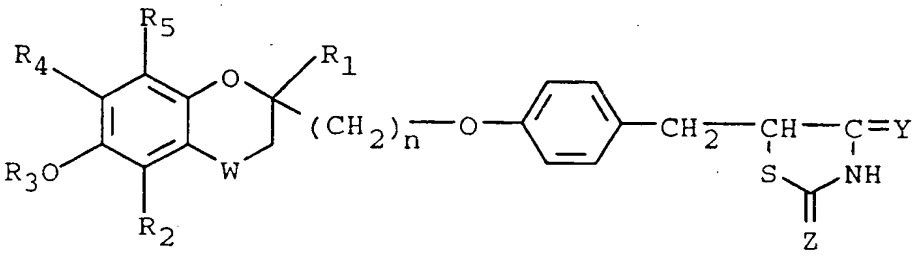
The 10 patients that are still on insulin have had a mean decrease of 45% (39 units) in their daily dose of insulin and appear to be continuing to reduce their insulin requirements. At the same time, their glycemic control is improving with a mean decrease of 15% (36 mg/dL) in blood glucose.

This group of subjects have had a significant decrease in their total exogenous insulin requirements with an improvement in their glycemic control. Prior to this study, these patients were being treated in a tertiary care setting with appropriate patient education and aggressive glucose-control management. However, even with this type of management, glucose control was poor as evidenced by a mean HbA_{1c} of 11.8. This value underscores the fact that patients treated with insulin are in general, not well controlled in spite of the burden of insulin treatment.

All patients have had a decrease in their insulin doses with 7 patients being able to discontinue insulin completely. Of this latter group, 3/7 have fasting glucose levels within the desired range for diabetic control. Given the potential risk of increased atherosclerotic disease due to injecting large doses of exogenous insulin, the ability to decrease insulin use and improve glycemic control is important.

CLAIMS

1. A method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus, the method comprising administering to a patient a therapeutically effective amount of a compound of Formula I



I

wherein R_1 and R_2 are the same or different and each represents a hydrogen atom or a C_1-C_5 alkyl group;

R_3 represents a hydrogen atom, a C_1-C_6 aliphatic acyl group, an alicyclic acyl group, an aromatic acyl group, a heterocyclic acyl group, an araliphatic acyl group, a (C_1-C_6 alkoxy)carbonyl group, or an aralkyloxycarbonyl group;

R_4 and R_5 are the same or different and each represents a hydrogen atom, a C_1-C_5 alkyl group or a C_1-C_5 alkoxy group, or R_4 and R_5 together represent a C_1-C_4 alkylenedioxy group;

n is 1, 2, or 3;

W represents the -CH_2-, CO, or CH-OR_6 group (in which R_6 represents any one of the atoms or groups defined for R_3 and may be the same as or different from R_3); and

Y and Z are the same or different and each represents an oxygen atom or an imino (=NH) group;

and pharmaceutically acceptable salts thereof.

2. A method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus, the method comprising administering to a patient having noninsulin-dependent diabetes mellitus a therapeutically effective amount of a compound of Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

3. The method of Claim 2 comprising administering to the patient a therapeutically effective amount of a compound of Formula wherein Y and Z are oxygen.

4. The method of Claim 2 comprising administering to the patient a therapeutically effective amount of a compound of Formula I wherein W is $-CH_2-$.

5. The method of Claim 2 comprising administering to the patient a therapeutically effective amount of a compound of Formula wherein n is 1.

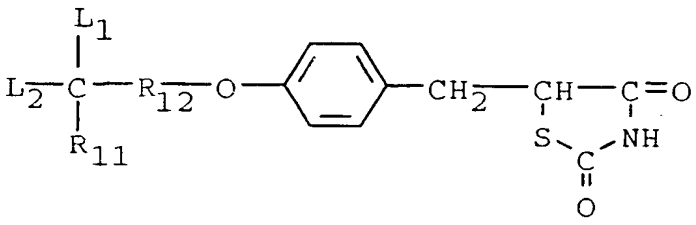
6. The method of Claim 2 comprising administering to the patient a therapeutically effective amount of a compound of Formula I wherein R_1, R_2, R_4, and R_5 are lower alkyl and R_3 is H.

7. The method of Claim 2 comprising administering to the patient a therapeutically effective amount of a compound of Formula I wherein Z and Y are oxygen, n is 1, and W is $-CH_2-$.

8. The method of Claim 2 comprising administering to the patient a therapeutically effective amount of a compound of Formula I wherein the compound is

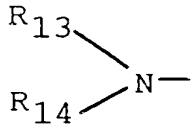
5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione.

9. A method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus, the method comprising administering to a patient having noninsulin-dependent diabetes mellitus a therapeutically effective amount of a compound of Formula II



II

wherein R_{11} is substituted or unsubstituted alkyl, alkoxy, cycloalkyl, phenylalkyl, phenyl, aromatic acyl group, a 5- or 6-membered heterocyclic group including 1 or 2 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, or a group of the formula



wherein R_{13} and R_{14} are the same or different and each is lower alkyl or R_{13} and R_{14} are combined to each other either directly or as interrupted by a heteroatom selected from the group consisting of nitrogen, oxygen, and sulfur to form a 5- or 6-membered ring;

wherein R_{12} means a bond or a lower alkylene group; and

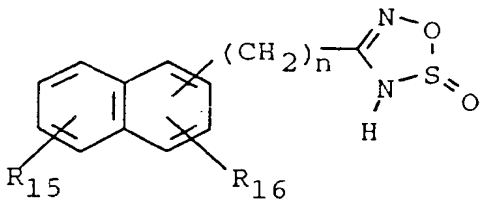
wherein L_1 and L_2 are the same or different and each is hydrogen or lower alkyl or L_1 and L_2 are combined to form an alkylene group, or a pharmaceutically acceptable salt thereof.

10. A method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus, the method comprising administering to a patient having noninsulin-dependent diabetes mellitus a therapeutically effective amount of a compound according to Claim 9 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

11. The method of Claim 10 comprising administering to the patient a therapeutically effective amount of a compound of Formula II wherein the compound is pioglitazone.

12. The method of Claim 10 comprising administering to the patient a therapeutically effective amount of a compound of Formula II wherein the compound is ciglitazone.

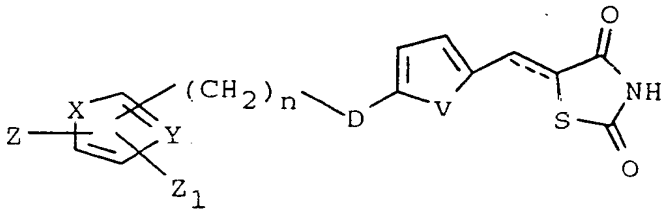
13. A method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus, the method comprising administering to a patient having noninsulin-dependent diabetes mellitus a therapeutically effective amount of a compound of Formula III



III

wherein R_{15} and R_{16} are independently hydrogen, lower alkyl containing 1 to 6 carbon atoms, alkoxy containing 1 to 6 carbon atoms, halogen, ethynyl, nitrile, methylthio, trifluoromethyl, vinyl, nitro, or halogen substituted benzyloxy; n is 0 to 4 and the pharmaceutically acceptable salts thereof.

14. A method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus, the method comprising administering to a patient having noninsulin-dependent diabetes mellitus a therapeutically effective amount of a compound of Formula IV



IV

wherein the dotted line represents a bond or no bond;

V is -CH = CH-, -N = CH-, -CH = N- or S;

D is CH_2, CHOH, CO, C = NOR_{17} or CH = CH;

X is S, O, NR_{18}, -CH = N or -N = CH;

Y is CH or N;

Z is hydrogen, (C_1-C_7) alkyl, (C_3-C_7)cycloalkyl, phenyl, naphthyl, pyridyl, furyl, thienyl, or phenyl mono- or disubstituted with the same or different groups which are

(C_1-C_3)alkyl, trifluoromethyl, (C_1-C_3)alkoxy, fluoro, chloro, or bromo;

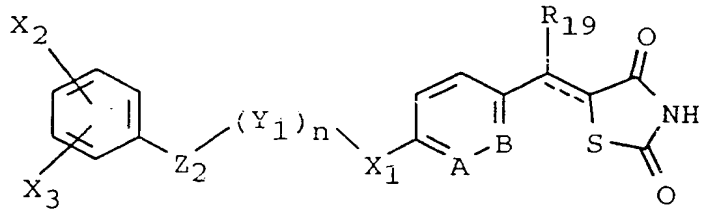
Z_1 is hydrogen or (C_1-C_3)alkyl;

R_{17} and R_{18} are each independently hydrogen or methyl; and n is 1, 2, or 3;

the pharmaceutically acceptable cationic salts thereof;

and the pharmaceutically acceptable acid addition salts thereof when the compound contains a basic nitrogen.

15. A method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus, the method comprising administering to a patient having noninsulin-dependent diabetes mellitus a therapeutically effective amount of a compound of Formula V



V

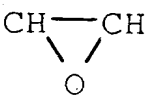
wherein the dotted line represents a bond or no bond;

A and B are each independently CH or N, with the proviso that when A or B is N, the other is CH;

X_1 is S, SO, SO_2, CH_2, CHOH, or CO;

n is 0 or 1;

Y_1 is CHR_{20} or R_{21}, with the proviso that when n is 1 and Y_1 is NR_{21}, X_1 is SO_2 or CO;

Z_2 is CHR_{22}, CH_2CH_2, CH=CH,  , OCH_2, SCH_2, $SOCH_2$ or SO_2CH_2;

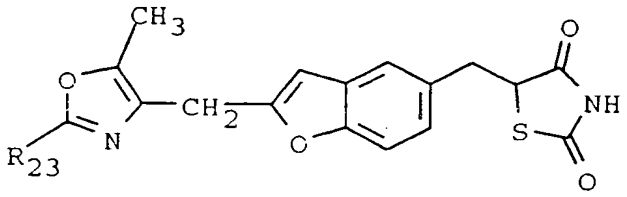
R_{19}, R_{20}, R_{21}, and R_{22} are each independently hydrogen or methyl; and

X_2 and X_3 are each independently hydrogen, methyl, trifluoromethyl, phenyl, benzyl, hydroxy, methoxy, phenoxy, benzyloxy, bromo, chloro, or fluoro;

a pharmaceutically acceptable cationic salt thereof;

or a pharmaceutically acceptable acid addition salt thereof when A or B is N.

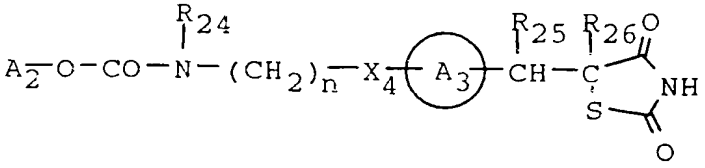
16. A method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus, the method comprising administering to a patient having noninsulin-dependent diabetes mellitus a therapeutically effective amount of a compound of Formula VI



VI

or a pharmaceutically acceptable salt thereof, wherein R_{23} is alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, phenyl, or mono- or disubstituted phenyl wherein said substituents are independently alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 3 carbon atoms, halogen, or trifluoromethyl.

17. A method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus, the method comprising administering a therapeutically effective amount of a compound of Formula VII



VII

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A_2 represents an alkyl group, a substituted or unsubstituted aryl group, or an aralkyl group wherein the alkylene or the aryl moiety may be substituted or unsubstituted;

A_3 represents a benzene ring having in total up to 3 optional substituents;

R_{24} represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group wherein the alkyl, or the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

or A_2 together with R_{24} represents substituted or unsubstituted C_{2-3} polymethylene group, optional substituents for the polymethylene group being selected from alkyl or aryl or adjacent substituents together with the methylene carbon atoms to which they are attached form a substituted or unsubstituted phenylene group;

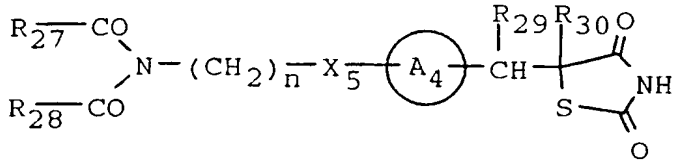
R_{25} and R_{26} each represent hydrogen, or R_{25} and R_{26} together represent a bond;

X_4 represents O or S; and

n represents an integer in the range of from 2 to 6.

18. A method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus, the method

comprising administering to a patient having noninsulin-dependent diabetes mellitus a therapeutically effective amount of a compound of Formula VIII



VIII

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate therefor, wherein:

R_{27} and R_{28} each independently represent an alkyl group, a substituted or unsubstituted aryl group, or an aralkyl group being substituted or unsubstituted in the aryl or alkyl moiety;

or R_{27} together with R_{28} represents a linking group, the linking group consisting of an optionally substituted methylene group and either a further optionally substituted methylene group or an O or S atom, optional substituents for the said methylene groups being selected from alkyl-, aryl, or aralkyl, or substituents of adjacent methylene groups together with the carbon atoms to which they are attached form a substituted or unsubstituted phenylene group;

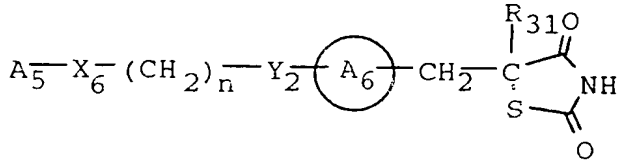
R_{29} and R_{30} each represent hydrogen, or R_{29} and R_{30} together represent a bond;

A_4 represents a benzene ring having in total up to 3 optional substituents;

X_5 represents O or S; and

n represents an integer in the range of from 2 to 6.

19. A method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus, the method comprising administering to a patient having noninsulin-dependent diabetes mellitus a therapeutically effective amount of a compound of Formula IX



IX

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A_5 represents a substituted or unsubstituted aromatic heterocyclyl group;

A_6 represents a benzene ring having in total up to 5 substituents;

X_6 represents O, S, or NR_{32} wherein R_{32} represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

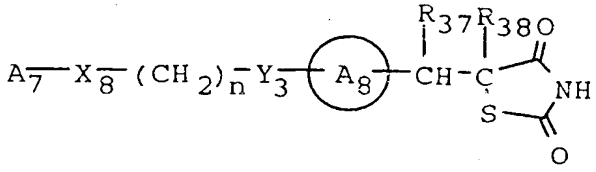
Y_2 represents O or S;

R_{31} represents an alkyl, aralkyl, or aryl group; and

n represents an integer in the range of from 2 to 6.

20. A method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus, the method comprising administering to a patient having noninsulin-dependent diabetes mellitus a

therapeutically effective amount of a compound of Formula X



X

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A_7 represents a substituted or unsubstituted aryl group;

A_8 represents a benzene ring having in total up to 5 substituents;

X_8 represents O, S, or NR_{39} wherein R_{39} represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

Y_3 represents O or S;

R_{37} represents hydrogen;

R_{38} represents hydrogen or an alkyl, aralkyl, or aryl group or R_{37} together with R_{38} represents a bond; and

n represents an integer in the range of from 2 to 6.

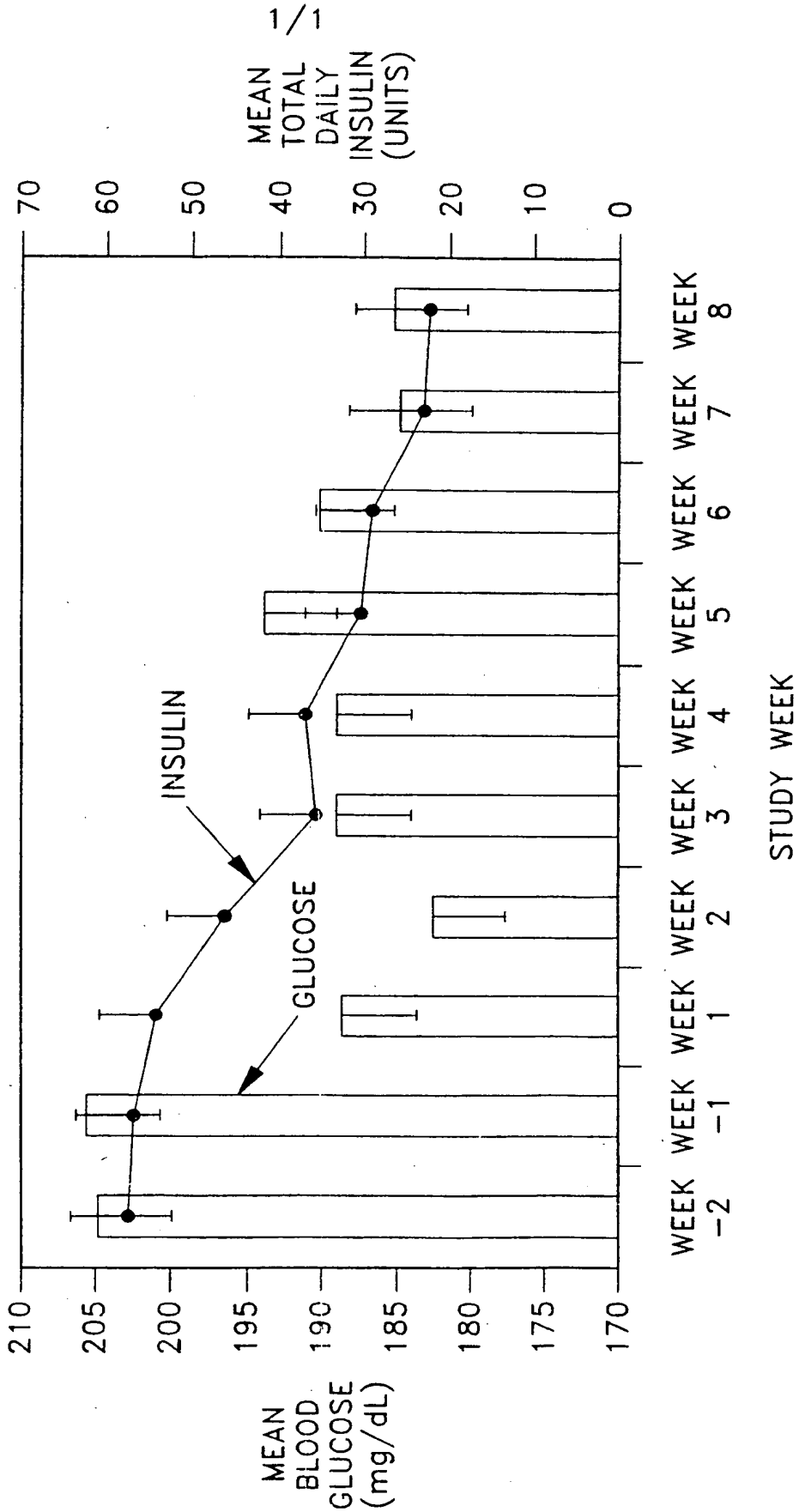
21. A method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus, the method comprising administering to a patient a therapeutically effective amount of:

[(±)-5-[(4-[2-Methyl-2-(pyridinylamino)-ethoxy]phenyl)methyl]-2,4-thiazolidinedione-(Z)-2-butenedioate;

englitazone; or

darglitazone.

FIG—1 MEAN (±SE) BLOOD GLUCOSE AND INSULIN USE (n=17)



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(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.

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(54) Title: A METHOD OF REDUCING THE AMOUNT OF EXOGENOUS INSULIN ADMINISTERED TO A PATIENT HAVING NONINSULIN-DEPENDENT DIABETES MELLITUS

(57) Abstract

This invention provides a method of reducing the amount of exogenous insulin administered to a patient having noninsulin-dependent diabetes mellitus by administering to a patient a therapeutically effective amount of a thiazolidione derivative and/or a related compound.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/12430

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 139 421 A (SANKYO CO) 2 May 1985 cited in the application see page 1, last paragraph - page 2, paragraph 1; claims 1-18	1-8
X	EP 0 277 836 A (SANKYO CO) 10 August 1988 cited in the application see page 1, line 1-19; claims 1-15	1-8
X	WO 95 07697 A (WARNER LAMBERT CO) 23 March 1995 see page 1, line 9-20 see page 39, line 1 - page 40, line 13 see claims 1-20	1-8

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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2

Date of the actual completion of the international search	Date of mailing of the international search report
25 October 1996	26.02.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Seegert, K

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DIABETES CARE, vol. 15, no. 8, 1992, pages 1075-1078, XP002016847 HOFMANN, C.A. ET AL: "New Oral Thiazolidinedione Antidiabetic Agents Act as Insulin Sensitizers" see page 1075, right-hand column, paragraph 1 ---	1-8
X	CURR. THER. RES. CLIN. EXP. (USA), vol. 55, no. 4, 1994, pages 416-421, XP002016848 ONUMA, T. ET AL: "The Effect of a New Oral Hypoglycemic Drug, CS-045, on Glucose Tolerance and Serum Lipids in Nonobese Japanese Patients with Non-Insulin-Dependent Diabetes Mellitus: A Pilot Study" see abstract ---	1-8
X	DIABETOLOGIA, vol. 37, no. suppl. 1, 1994, page a63 XP002016849 KUZUYA, T. ET AL: "One-Year Clinical Trial of a New Oral Hypoglycemic Agent, CS-045, in NIDDM Patients" see abstract ---	1-8
X	MED. HYG. (SWITZERLAND), vol. 53, no. 2053, 4 January 1995, pages 22-27, XP002016850 GERBER, P.: "Diabète" see page 27 ---	1-8
X	N. ENGL. J. MED. (UNITED STATES), vol. 331, no. 18, 1994, pages 1188-1193, XP002016851 NOLAN, J.J. ET AL: "Improvement in Glucose Tolerance and Insulin Resistance in Obese Subjects Treated with Troglitazone" see abstract see page 1188, left-hand column, last paragraph - page 1188, right-hand column, paragraph 2 --- -/--	1-8

2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 119, no. 1, 5 July 1993 Columbus, Ohio, US; abstract no. 97, "CS-045, an Ameliorator for Insulin Resistance" XP002016853 see abstract & DIABETES FRONT., vol. 3, no. 6, 1992, pages 570-574, KANAZAWA ET AL.: ---	1-8
X	ENDOCRINOL. METAB. CLIN. NORTH AM. (USA), vol. 21, no. 2, 1992, pages 329-350, XP002016852 KARAM, J.H.: "Type II Diabetes and Syndrome X" see page 344, paragraph 2 - page 346, paragraph 1 -----	1-8

INTERNATIONAL SEARCH REPORT

Ir national application No.
PCT/US 96/ 12430

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1) Claims 1-8, 2) Claims 9-12, 3) Claim 13, 4) Claim 14, 5) Claim 15, 6) Claim 16, 7) Claim 17, 8) Claim 18, 9) Claim 19, 10) Claim 20, 11) Claim 21

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-8

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/12430

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0139421	02-05-85	JP-C-	1604002	22-04-91
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		WO-A-	9507694	23-03-95
		US-A-	5478852	26-12-95